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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,030	06/29/2006	Krishna Murthy Ella	06-40104-US	7696

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	**PAPER NUMBER**
1648	

NOTIFICATION DATE	DELIVERY MODE
12/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phlipdocketing@reedsmith.com

Office Action Summary	Application No.	Applicant(s)	
	10/585,030	ELLA ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/13/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-4,6 and 8-18* is/are pending in the application.

5a) Of the above claim(s) *10,12 and 13* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4,6,8,9 and 14-18* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/10 has been entered.

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Claims 1-9 and 14-18 are examined on the merits.

Response to Arguments

Applicant's arguments with respect to claims 1-9 and 14-18 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(New Rejection) Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 17 recites, "...proteins are simultaneously prepared and purified." However, it is unclear how proteins can be prepared (i.e., produced and isolated from

yeast cells and purified (filtration, chromatography) since these steps are conducted at different stages (not simultaneously) of the procedure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(New Rejection Necessitated by Amendments) Claims 1-4, 6, 8, 9, 14-16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lakshmi et al. (Vaccine, 2000), Nielsen et al. (WO 03/050274), Nielsen et al. (WO 03/050274), da Costa et al. (Biotechnology Techniques, 1995) and Bitter et al. (Journal of Medical Virology, 1988).

A process for the preparation and purification of protein(s) comprising:

(a) lysing, in the absence of a detergent, vector cells (yeast) expressing said protein(s) to obtain a cell lysate;

(b) centrifuging the cell lysate between 1000g and 10,000g to form a supernatant portion and solid portion;

(c) obtaining the solid portion from step (b) wherein the solid portion comprises the protein(s);

(d) suspending the solid portion in a buffer of pH 6 to 7.5;

(e) forming an insoluble matrix after step (d) by the addition of divalent ionic salt having a concentration ranging from 0.2 % to 10% with counter ions of either phosphate, chloride and/or acetate solution to the suspension;

(f) subjecting the insoluble matrix to centrifugation to form a pellet;

(g) repeatedly subjecting the pellet from step (f) to a desorption process to release the protein(s) from said insoluble pellet by using either Tris buffer of pH 8.0 to 8.5 or Tris buffer with EDTA at pH 7.0 to 8.0; and

(h) recovering the protein{s) through hydrophobic chromatography.

The claimed invention also requires that steps (f)-(h) are not required, but the proteins are eluted with Tris buffer of a pH 8.0 to 8.5.

The protein can be a viral protein or not a viral protein. Examples of the viral proteins are viral antigens (Hepatitis B antigen), recombinant proteins and/or biotherapeutic proteins. In addition, when chromatography is used, purified fractions containing the proteins are pooled for diafiltration and/or for sterile filtration. The divalent cation of the salt is Zn, Ca, Mg or a combination thereof. In addition, the proteins are highly purified without the loss of biological activity

Lakshmi et al. teach the production of recombinant Hepatitis B surface antigen (HBsAg). They use yeast cells to produce the recombinant HBsAg. The process used by Lakshmi et al. involves culturing yeast, centrifuging the yeast, precipitating the HBsAg with PEG, exposing the HBsAg to hydrophobic interactions, processing the HBsAg through ion-exchange

chromatography, subjecting the HBsAg elution to ultrafiltration and sterile filtration and formulating the sterile, filtered composition of HBsAg. (see page 2010)

However, Lakshmi et al. do not teach that the yeast are lysed; forming an insoluble matrix with a divalent salt at a concentration of 0.2 to 10% with counter ions of phosphate, chorlide or acetate; or repeatedly subjecting the centrifuged pellet to a desorption process that releases the proteins by using Tris buffer of pH 8.0 to 8.5 or Tris buffer with EDTA at pH 7.0 to 8.0.

Nielsen et al. teach the use of salts in the coagulation (forming an insoluble matrix) of yeast produced products during fermentation. These salts include divalent salts at a concentration range of 0.2-20% w/w. [see page 5] These salts can have counter ions of chloride. Nielsen et al. also state that non-viral proteins can be produced by the fermented yeast, such as therapeutic proteins (i.e., insulin) [see page 1].

da Costa et al. teach the production of a mycobacterium protein from yeast cells and the subsequent processing of isolated protein. da Costa et al. teach the use of Tris buffer to desorb the mycobacterium proteins in order to improve yields of the protein. [see page 528]

Bitter et al. teach the production of HBsAg in yeast cells through a fermentation protocol. In order to obtain the HBsAg proteins, Bitter et al. teach that yeast cells were subjected to agitation with glass beads in order to lyse the cells and the resulting supernatant was recovered. [see page 124]

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Lakshmi et al. in order to produce and purify proteins from yeast cells according to the

claimed method. One would have been motivated to do so, given the suggestion by Lakshmi et al. that a multi-step method can be used to purify HBsAg, including the centrifugation, precipitation, chromatography and filtration. There would have been a reasonable expectation of success, given the knowledge that divalent salts can be used at the claimed concentration in order to coagulate yeast products, as taught by Nielsen et al., also given the knowledge that during desorption of yeast produce proteins, Tris buffer can be used, as taught by da Costa et al., and also given the knowledge that yeast produced proteins can be obtained at a higher concentration if the yeast cells are lysed through agitation with glass beads, as taught by Bitter et al. MPEP § 2144.05 (II) (A) states, "...*Optimization Within Prior Art Conditions or Through Routine Experimentation*..."[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation...". Therefore, while the specific pH of the Tris buffers are not discussed by the cited art, since the intended use of the HBsAg is for *in vivo* administration, the pH would be a near neutral pH (e.g., 6.0 to 8.0) and since the prior art teaches the use of desorption in the use of processing yeast produce proteins, one of ordinary skill in the art would optimize the number of times desorption was used in the processing of proteins. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BENJAMIN P BLUMEL/
Primary Examiner, Art Unit 1648